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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,215	10/02/2003	Roland Callens	05129-00072-US	9641

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EXAMINER

KOSAR, ANDREW D

ART UNIT PAPER NUMBER

1654

DATE MAILED: 06/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/677,215	Applicant(s) CALLENS ET AL.	
	Examiner Andrew D. Kosar	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 March 2006 and 31 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 8,13-22,29 and 33-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7,9-12,23-28 and 30-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>20060531</u> |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/02/03</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION***Election/Restrictions***

Applicant's election with traverse of Group IV (claims 1-12 and 23-32) and the species of A being PheLeuGly, in the reply filed on March 23, 2006 is acknowledged. The traversal is on the ground(s) that Applicant asserts that it would not be an undue burden to search all of the claims. This is not found persuasive because the examiner set forth a proper *prima facie* case and as stated in the Restriction requirement, it would be an undue burden because the search for the method of making the compounds of Group IV would not lead to the discovery of methods of making another compound nor would it lead to the discovery of compounds that are not made by the method.

During a telephone conversation with Applicant's representative, Ashley Pezzner, on May 31, 2006, a provisional election was made with traverse to complete the requirement for a single species, affirming the election of A and further electing R¹ and R² to be H, thus the species elected being GlyPheLeuGly, readable upon claims 1-7, 9-12, 23-28 and 30-32. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8, 13-22, 29 and 33-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

Sequence Compliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821-1.825 for

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the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR §§ 1.821- 1.825) in order to effect a complete response to this office action.

Specifically, Sequences are present which require SEQ ID NOs at page 1, line 11; page 4, lines 17 and 18; page 11, lines 1 and 2; and page 14, line 1.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio
(<http://www.uspto.gov/ebs/efs/downloads/documents.htm>), EFS Submission User Manual – ePave)

2. US Postal Service:

Commissioner for Patents

PO Box 22313-1450

Alexandria, VA 22313-1450

3. Hand carry, Federal Express, United Parcel Service, or other delivery service:

U.S. Patent and Trademark Office

Mail Stop Sequence

Customer Window, Randolph Building

401 Dulany Street

Alexandria, VA 22314

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on October 4, 2002. It is noted, however, that applicant has not filed a certified copy of the FR 02.12493 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

Applicant's IDS submitted October 10, 2003 has been considered. References not in English have been considered to the extent of the supplied English abstract and/or English equivalent document. Page 4 of EP 0678501 A1 has not been provided and thus the reference has not been considered. In the interest of compact prosecution, and because the Examiner relies

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upon the reference in the rejection set forth below, the Examiner has included the reference on the attached PTO-892.

Specification

The disclosure is objected to because of the following informalities:

The chemical formula on page 12, lines 23-25 has the carbonyl O attached at the incorrect carbon atom.

Additionally, sequences are present which require SEQ ID NOs at page 1, line 11; page 4, lines 17 and 18; page 11, lines 1 and 2; and page 14, line 1.

Appropriate correction is required.

Claim Objections

Claims 1, 7, 9 and 10 are objected to because of the following informalities:

Claims 1, 7, 9 and 10 recite 'denotes' which would more clearly recite 'is', so as to conform with similar recitations, e.g. claim 6, "the compound of general formula (III) is aqueous ammonia".

Claims 9 recites the same generic chemical formula, however they refer to it by two different formula numbers, (VI) and (V), respectively. It is noted that prior to claim 9, no formula (V) is present, and only (I)-(IV) are used.

Claims 9 recites, "a fragment C", which would more clearly recite via usage of another identifier, e.g. Q, Z, X', etc., as C is generally reserved for use in identifying carbon.

Additionally, claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent

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form, or rewrite the claim(s) in independent form. Claim 9 should designate that the method of claim 1 further comprises the recited step, as dependent claims must be further limiting.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7, 9-12, 23-28 and 30-32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instant claims are asserted to be, “of use, for example, as medicinal products, as intermediates for producing peptides and as a spacer arm in pharmaceutical compositions intended to take biologically active principles specifically to certain cells of the body.” (page 1, *Specification*). In the instant case, the utility is a 'general utility' (*see MPEP § 2107.01(I)*, “[I]ndicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target”; “A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.”).

Further, the MPEP states that the following categories are not substantial utilities: (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in

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which the material is involved; (B) A method of treating an unspecified disease or condition; (C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility; (D) A method of making a material that itself has no specific, substantial, and credible utility; and (E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility. MPEP § 2107.01(I).

Specifically, the method is within the parameters of item(s) (D) and/or (E), and thus the product has no substantial utility, as the method make a product that is either an intermediate for making another peptide (which is unidentified in the instant specification) or as a linker between two esoteric components of a drug delivery system.

Further, the MPEP states, "An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention." MPEP § 2107.01(I).

Additionally, the art recognizes no specific or substantial utility for the compound(s) of the invention. For example, SMALES (PTO-1449, 10/02/03) states that, with regards to the elected peptide, that there is, "a considerable volume of literature on the possible use of peptides as components of drug delivery systems. (page 1558). Smales does not provide a specific or substantial utility, but rather asserts that there are possibilities for peptides as components of drug delivery systems without naming any of the 'possibilities'.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-12, 23-28 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear and indefinite as it recites, "Y is chosen from H and cations", however Y is attached as COOY which does not designate any charge in the claims, and thus it is unclear whether Y is a cation before binding to carboxylic acid, or whether it is a cation that forms a salt of the carboxylic acid, i.e.- COO⁻Y⁺. For example, *t*-butyl cation is used in forming a carboxylic acid ester.

Claim 1 recites, "HN-A-COOH" and "HN-A-COOY" for formulae (I) and (II) where A 'denotes a peptide chain', however in view of the specification, it is unclear whether the recitation "HN-A-COOH" is defining a peptide as a unit (NH-CHR-COO)_{n≥2}, or whether A alone is a peptide chain attached to an NH and a COOH at the termini, i.e. NH-(NH-CHR-CO)_{n≥2}-COO or NH-(CO-CHR-NH)_{n≥2}-COO, and thus the claims are indefinite.

Claim 1 recites, "R¹ and R² together form a cycloalkyl", however it is unclear how they can form anything other than a heterocycle, as they are attached to a nitrogen and would necessarily require that it be part of any cyclic structure formed, and thus the claims are indefinite.

Claims 9 recites, "HN-B" in formula (VI) and B 'denotes an amino acid or a peptide', however, it is unclear whether the HN moiety is from B, i.e. the N-terminus of the amino acid/peptide, or separately attached to the N-terminus i.e. NH-(NH-CHR-CO) or NH-(CO-CHR-

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NH), and thus the claims are indefinite. Further, it is unclear whether the formula variables are the same, or different, than those of the independent claim from which it depends.

Claim Rejections - 35 USC § 103

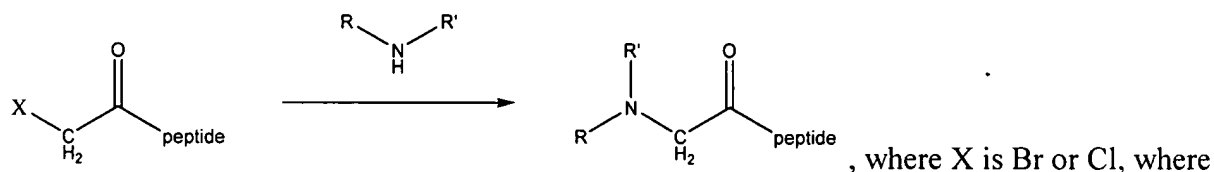
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9, 10, 12, 23-28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over SMALES (PTO-1449, 10/02/03) in view of MARINZI (C. Marinzi, et al. Bioorg. Med. Chem. (2001) 9, pages 2323-2328), SAHA (U.K. Saha and R. Roy. Tetrahedron Letters (1995) 36(21), pages 3635-3638) and MIMURA (US Patent 6,197,998 B1).

The instant claims are drawn to a method of making compounds via the general reaction scheme:



the product is the tetrapeptide GFLG and the amine is ammonia.

Smales teaches the peptide GFLG (e.g. Scheme Page 1558).

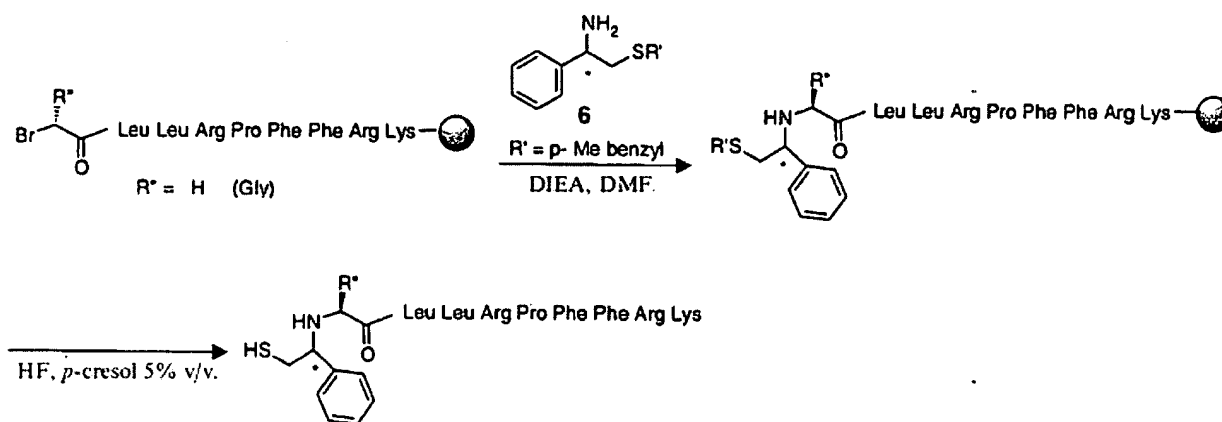
The difference between Smales and the instant claims is that while Smales teaches the

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product, Smales does not teach the synthesis as instantly claimed.

The art recognizes reactions of various amines with haloacetylated amino acids, peptides and peptoides to generate N-Gly-peptides (e.g. Canne and Amatsu (EP 0687501A1) which are cited to show the state of the art).

Marinzi teaches synthesis of N^α-substituted Gly-Peptide using bromoacetylated peptides:



(page 2324, Scheme 1) and further teaches that the method is an “easy and quantitative route for the derivatization of the peptide” (page 2325).

Saha teaches synthesis of peptoids, N-substituted polyglycine peptides, using bromoacetylated submonomers in the reaction (e.g. Scheme 2, page 3636). The synthesis is conducted without a resin (solution phase).

Mimura teaches synthesis of chloroacetyltyrosine (Example 1, column 4) and synthesis of GlyTyr via reaction of chloroacetyltyrosine with 28% aqueous ammonia (Example 2, column 5). Mimura teaches that the synthesis of this dipeptide via this mechanism is favored because the product can be formed in “one step in high yields.” (column 3, lines 52-53).

It would have been obvious to have made the peptide of Smales, or any other peptide, via reaction of the haloacetylated fragment with ammonia or any substituted amine, in order to form the final product more efficiently with fewer steps and higher yields.

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One would have been motivated to have made any peptide, including the peptide GFLG, from the haloacetylated form in order to have an easy and quantitative route for derivitizing peptides and to reduce the number of steps in the process, such as protection/deprotection steps, increase the efficiency of the production and the yield of the product.

One would have had a reasonable expectation for success in forming the product via reaction of the haloacetylated tripeptide with ammonia, as the art recognizes that the reaction of ammonia with haloacetylated amino acids and the reaction of amines with haloacetylated peptides of any size, both on a resin and in solution phase.

Additionally, one would have been motivated to have repeated the steps in order to

Further, with regards to the temperature and concentration ranges, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. temperature ranges, concentration of reactants), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP § 2145.05). One would have been motivated to optimize the conditions in order to achieve the most efficient reaction possible, with a reasonable expectation for success, as they are art recognized variables that are routinely determined and optimized.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Please note, the limitations of claims 9 and 10 are met in that the claimed method steps comprise reacting 'a fragment of formula (V)' with C. The broadest reasonable interpretation includes, but is not limited to, reaction of one amino acid with a dipeptide followed by a reaction to generate the haloacetyl moiety, as 'comprising' does not preclude the presence of other steps, and additionally, the broadest reasonable interpretation of 'a fragment of' includes, e.g. B alone.

Claims 1-7, 9-12, 23-28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over SMALES (PTO-1449, 10/02/03) in view of MARINZI, SAHA and MIMURA, as applied to claims 1-7, 9, 10, 12, 23-28 and 30-32, *supra*, and in further view of ANTEUNIS (US Patent 4,725,645; PTO-1449, 10/02/03).

The instant claims are presented *supra*, and are further drawn to the method where the reactant forming products of formula (II) are activated with persilylation.

The teachings of Smales, Marinzi, Saha and Mimura are presented *supra*.

Anteunis teaches using silylated amino acids during peptide synthesis, "makes it possible to carry out a rapid coupling reaction in continuous fashion, which reaction takes place without racemisation and can be carried out in the absence of basic coreagents, with water optionally present and in the presence of known protecting agents. In addition, it enables peptides of high molecular weight to be produced in yields higher than those obtained with the known silylating agents. Moreover, the process of the invention enables the water to be chemically consumed and volatile silyl derivatives to be obtained, which facilitates the removal of the later (column 1, line 60 to column 2, line 3).

It would have been obvious to have used silyl activated peptides or amino acids to form the building blocks in order achieve rapid coupling reactions between the subunits.

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One would have been motivated to silyl activate the peptides in order to increase the speed and efficiency of the reaction and reduce racemization of the product.

One would have had a reasonable expectation for success in forming the starting material by reaction of silyl activated peptides, as silyl activation and the subsequent use in the synthesis of peptides is a widely practiced technique that can be used to make any peptide.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion


NO CLAIMS ARE ALLOWED.

The prior art made of record on the attached PTO-892 and not relied upon in any rejection is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Andrew D. Kosar, Ph.D.
Art Unit 1654


Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600

Notice to Comply	Application No. 10677215	Applicant(s) CALLENS ET AL.	
	Examiner Andrew D. Kosar	Art Unit 1654	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923

For CRF Submission Help, call (703) 308-4212 or 308-2923

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